Central Role of P2Y6 UDP Receptor in Arteriolar Myogenic ToneHighlights

Titre	Central Role of P2Y6 UDP Receptor in Arteriolar Myogenic ToneHighlights
Type de publication	Article de revue
Auteur	Kauffenstein, Gilles [1], Tamareille, Sophie [2], Prunier, Fabrice [3], Roy, Charlotte [4], Ayer, Audrey [5], Toutain, Bertrand [6], Billaud, Marie [7], Isakson, Brant E [8], Grimaud, Linda [9], Loufrani, Laurent [10], Rousseau, Pascal [11], Abraham, Pierre [12], Procaccio, Vincent [13], Monyer, Hannah [14], de Wit, Cor [15], Boeynaems, Jean-Marie [16], Robaye, Bernard [17], Kwak, Brenda R [18], Henrion, Daniel [19]
Pays	Etats-Unis
Editeur	American Heart Association
Ville	Dallas
Type	Article scientifique dans une revue à comité de lecture
Année	2016
Langue	Anglais
Date	02 juin 2016
Numéro	8
Pagination	1598-1606
Volume	36
Titre de la revue	Arteriosclerosis, Thrombosis, and Vascular Biology
ISSN	1079-5642
Mots-clés	Myocytes [20], myogenic tone [21], myosin light chains [22], nucleotides [23], purinoceptor P2Y6 [24], rhoA GTP-binding protein [25], smooth muscle [26]

Résumé en anglais	OBJECTIVE: Myogenic tone (MT) of resistance arteries ensures autoregulation of blood flow in organs and relies on the intrinsic property of smooth muscle to contract in response to stretch. Nucleotides released by mechanical strain on cells are responsible for pleiotropic vascular effects, including vasoconstriction. Here, we evaluated the contribution of extracellular nucleotides to MT. APPROACH AND RESULTS: We measured MT and the associated pathway in mouse mesenteric resistance arteries using arteriography for small arteries and molecular biology. Of the P2 receptors in mouse mesenteric resistance arteries, mRNA expression of P2X1 and P2Y6 was dominant. P2Y6 fully sustained UDP/UTP-induced contraction (abrogated in P2ry6(-/-) arteries). Preventing nucleotide hydrolysis with the ectonucleotidase inhibitor ARL67156 enhanced pressure-induced MT by 20%, whereas P2Y6 receptor blockade blunted MT in mouse mesenteric resistance arteries and human subcutaneous arteries. Despite normal hemodynamic parameters, P2ry6(-/-) mice were protected against MT elevation in myocardial infarction-induced heart failure. Although both P2Y6 and P2Y2 receptors contributed to calcium mobilization, P2Y6 activation was mandatory for RhoA-GTP binding, myosin light chain, P42-P44, and c-Jun N-terminal kinase phosphorylation in arterial smooth muscle cells. In accordance with the opening of a nucleotide conduit in pressurized arteries, MT was altered by hemichannel pharmacological inhibitors and impaired in Cx43(+/-) and P2rx7(-/-) mesenteric resistance arteries. CONCLUSIONS: Signaling through P2 nucleotide receptors contributes to MT. This mechanism encompasses the release of nucleotides coupled to specific autocrine/paracrine activation of the uracil nucleotide P2Y6 receptor and may contribute to impaired tissue perfusion in cardiovascular diseases
URL de la notice	http://okina.univ-angers.fr/publications/ua15150 [27]
DOI	10.1161/ATVBAHA.116.307739 [28]
Lien vers le document	http://atvb.ahajournals.org/content/36/8/1598 [29]
Titre abrégé	Arterioscler. thromb. vasc. biol.

Liens

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